



Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Tenofovir Disoproxil Fumarate (Viread, TDF)

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Tenofovir disoproxil fumarate (TDF) is an orally bioavailable form of tenofovir (TFV). For information about tenofovir alafenamide (TAF), see the [TAF section](#).

Animal Studies

Carcinogenicity

TFV was mutagenic in one of two *in vitro* assays and has shown no evidence of clastogenic activity. Long-term oral carcinogenicity studies of TFV were carried out at 16 times (in mice) and five times (in rats) the exposure seen in humans who received the standard dose. In female mice, the incidence of liver adenomas was increased at exposures that were 16 times those observed in humans who received therapeutic doses. In rats, there was no evidence of carcinogenicity at exposures up to five times those observed in humans who received the therapeutic dose.¹

Reproduction/Fertility

Reproduction studies have been performed using doses of TFV up to 14 times (in rats) and 19 times (in rabbits) the human dose, based on body surface area comparisons. The use of TFV was not associated with impaired fertility or harm to the fetus in these studies. There were also no effects on fertility, mating performance, or early embryonic development when TFV was administered (at a dose of 600 mg/kg per day; equivalent to 10 times the human dose based on body surface area) to male rats for 28 days before mating, and to female rats from 15 days before mating through Day 7 of gestation. However, an alteration of the estrous cycle in female rats was observed.¹

Teratogenicity/Adverse Pregnancy Outcomes

Fetal monkeys with chronic, high-level exposure to TFV that was equivalent to 25 times the area under the curve [AUC] achieved with therapeutic dosing in humans had lower fetal circulating insulin-like growth factor (IGF)-1, higher IGF binding protein-3 levels, and lower body weights than TFV-unexposed fetal monkeys. A slight reduction in fetal bone porosity was also observed in TFV-exposed fetal monkeys. These effects were observed within 2 months of maternal treatment.¹

Placental and Breast Milk Passage

Intravenous administration of TFV to pregnant cynomolgus monkeys resulted in a fetal/maternal plasma ratio of 0.17, demonstrating that TFV crosses the placenta.²

Human Studies in Pregnancy

Pharmacokinetics

In a retrospective population pharmacokinetic study of 46 pregnant women and 156 nonpregnant women who were receiving combination regimens that included TDF, pregnant women had a 39% higher apparent clearance of TFV than nonpregnant women. Apparent clearance decreased slightly but significantly with increasing age.³ In the P1026s study of 37 women who received TDF-based combination therapy during pregnancy and postpartum, the percentage of women with TFV AUC that exceeded the target of 1.99 µg·hour/mL (the 10th percentile in nonpregnant adults) was lower at 30 to 36 weeks gestation (73%, 27 of 37 women) than at 6 to 12 weeks postpartum (84%, 27 of 32 women). TFV trough levels and AUC were 17% to 20% lower during the third trimester compared to postpartum. The median weight of the women below the target exposure (97.9 kg) was significantly higher than the median weight of the women who met the target exposure (74.2 kg).⁴

In another study of 34 women who received TDF plus emtricitabine (FTC) in the third trimester and postpartum, TFV AUC, peak concentration, and trough concentration were all about 25% lower in pregnant women than in postpartum women, but these decreased exposures were not associated with virologic failure.⁵ In a study of women who did not have HIV and who were using TDF as part of pre-exposure prophylaxis (PrEP), intracellular concentrations of tenofovir diphosphate (TFV-DP) in pregnant women were about 70%

of those in nonpregnant women, even after adjusting for adherence.⁶ In pregnant women who had hepatitis B virus (HBV) infection but who did not have HIV infection, the estimated geometric mean TFV AUC_{0-24h} was 20% lower during pregnancy (95% confidence interval [CI], 19% to 21%) than during the postpartum period. There were no cases of perinatal HBV transmission in this study.⁷

Thus, in light of only modestly lower TFV exposure during pregnancy without evidence of adverse impact on virologic efficacy, standard dosing of TDF during pregnancy continues to be recommended.

Placental and Breast Milk Passage

In studies of pregnant women who were receiving chronic TDF, the cord blood-to-maternal-plasma ratio of TFV ranged from 0.60 to 1.03, indicating high placental transfer.^{4,5,8,9} In studies of pregnant women who received single-dose TDF (with and without FTC) during labor, the median cord blood-to-maternal-plasma ratio of TFV at delivery ranged from 0.55 to 0.73.^{10,11} Intracellular TFV concentrations were detected in the peripheral blood mononuclear cells from cord blood in all infants after a single maternal dose of TDF 600 mg with FTC 400 mg, but intracellular TFV-DP was detectable in only two of 36 infants (5.5%).¹²

In a study of 50 breastfeeding women without HIV who received TDF/FTC (under directly observed therapy for 10 days) as PrEP, median peak and trough time-averaged TFV breast milk concentrations were similar at 3.2 ng/mL (interquartile range [IQR] 2.3–4.7) and 3.3 ng/mL (IQR 2.3–4.4), respectively. The infant plasma TFV concentration was unquantifiable (<0.31 ng/mL) in 46 of 49 infants (94%); in the three infants with detectable TFV concentrations, the level was 0.9 ng/mL in two and 17.4 ng/mL in one. Based on this study's results, the median TFV dose ingested through breast milk was estimated to be 0.47 mcg/kg, or <0.01% of the proposed daily pediatric dose of TDF 6 mg/kg.¹³ In a study of 59 breastfeeding women with HIV who received TDF/lamivudine (3TC)/efavirenz (EFV) in Uganda and Nigeria, no infant had detectable TFV in plasma after observed dosing.¹⁴

Reproduction/Fertility

In a retrospective analysis of 7,275 women who were receiving antiretroviral therapy (ART) (1,199 of whom were receiving regimens that contained TDF), women who used TDF had a slightly lower pregnancy rate than women who did not use TDF. However, the findings were limited by the observational nature of the data, and additional studies are needed for confirmation.¹⁵ A trial in Kenya and Uganda randomized participants who did not have HIV but whose sexual partners had HIV (serodiscordant heterosexual couples) to receive daily TDF, TDF/FTC, or placebo for PrEP. Pregnancy incidence was not significantly different among the arms: pregnancy incidence per 100 patient-years was 10.0 among women assigned to receive placebo, 11.9 among those assigned to receive TDF ($P = 0.22$ vs. placebo), and 8.8 among those assigned to receive TDF/FTC ($P = 0.39$ vs. placebo).¹⁶

Teratogenicity

In a study of 431 pregnancies that occurred during an HIV PrEP trial in which women who did not have HIV were randomized to receive placebo, TDF, or TDF plus FTC, there was no difference in risk of congenital anomalies between the TDF-containing arms and placebo arms.¹⁶ No association was seen between maternal TDF use and the occurrence of birth defects among offspring in three large U.S. cohorts of children born to women with HIV: PACTG 219/219C ($n = 2,202$, with 214 first-trimester TDF exposures), P1025 ($n = 1,112$, with 138 first-trimester TDF exposures),^{17,18} and PHACS ($n = 2,580$, with 431 first-trimester TDF exposures).¹⁹ In the French Perinatal Cohort, no association was found between birth defects and the use of TDF, with a power of 70% for an odds ratio of 1.5 ($n = 13,124$, with 823 first-trimester TDF exposures).²⁰ Among 382 pregnancies that occurred in 302 women in Uganda and Zimbabwe who participated in the DART trial—approximately two-thirds of whom received TDF for >90% of their pregnancies—TDF use was not associated with birth defect risk.²¹

Finally, in the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to TDF have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a two-fold increase in the risk of birth defects in the cardiovascular and genitourinary systems. No increase in birth

defects has been observed with TDF. Among the cases of first-trimester TDF exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.36% (91 of 3,851 births; 95% CI, 1.91% to 2.89%), compared with a total prevalence of 2.72% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.²²

In summary, there is no evidence that the use of TDF increases the risk of birth defects.

Adverse Pregnancy Outcomes

Overall Adverse Pregnancy Outcomes

In an observational study in Botswana of >11,000 births among women with HIV who received ART during pregnancy and gave birth between August 2014 and August 2016, the risk of any adverse birth outcome (i.e., stillbirth, neonatal death, preterm delivery or very preterm delivery, small for gestational age [SGA] or very small for gestational age) was lower in women who received TDF/FTC/EFV than in women who received any other regimen (TDF/FTC plus nevirapine [NVP], adjusted relative risk [ARR] 1.15; TDF/FTC plus lopinavir/ritonavir [LPV/r], ARR 1.31; zidovudine [ZDV]/3TC plus NVP, ARR 1.30; ZDV/3TC plus LPV/r, ARR 1.21). Furthermore, among infants who were exposed to ART from conception, TDF/FTC/EFV was associated with lower risk for adverse birth outcomes than other antiretroviral (ARV) regimens.²³

Fetal Growth Effects

In the PHACS study from the United States, 449 of the 2,029 infants (21%) who were exposed to HIV but who were uninfected had *in utero* exposure to TDF. TDF-exposed infants and infants without exposure to TDF had similar rates of low birth weight (LBW) and SGA and similar newborn length-for-age and head circumference-for-age z-scores (LAZ and HCAZ, respectively).²⁴ In a different U.S. cohort study, P1025, maternal TDF use was similarly not associated with differences in body size parameters at birth.²⁵ In a combined analysis of data from 4,646 births that occurred during the PHACS and P1025 studies, there were no differences in the risks of LBW infants (<2,500 g) and very LBW infants (<1,500 g) for women who received TDF/3TC plus LPV/r and those who received ZDV/3TC plus LPV/r during pregnancy.²⁶ **In a European cohort study (EPICC), the use of TDF was similarly not associated with SGA infants.**²⁷ However, in a Dutch study of 74 HIV-exposed infants (including nine with *in utero* TDF exposure), maternal TDF use was linked to an increased risk of LBW (<2,500 g).²⁸

In the largely Africa-based PROMISE trial, pregnant women with HIV but without advanced disease or immunosuppression (defined as CD4 T lymphocyte counts ≥ 350 cells/mm³) were randomized at ≥ 14 weeks gestation (with a median of 26 weeks gestation) to receive ZDV alone, ZDV/3TC plus LPV/r (ZDV-based ART), or TDF/FTC plus LPV/r (TFV-based ART). The TFV-based ART arm and ZDV-based ART arms showed no significant differences in the incidence of LBW infants (<2,500 g; 16.9% vs. 20.4%, $P = 0.3$).²⁹ **In the large observational study in Botswana, the use of TDF/FTC/EFV was associated with a lower risk of SGA infants than all other regimens.**²³ A fetal ultrasound study in South Africa demonstrated no association between duration of maternal TDF use and long-bone (femur and humerus) growth in the infant.³⁰ This same research group also demonstrated that the duration of *in utero* TFV exposure was not related to infant length at birth.³¹

Additionally, a placebo-controlled trial of TDF 300 mg that was initiated at 28 weeks gestation in Thai women with HBV (but not HIV) permits an assessment of the potential impact of TDF on birth outcomes when TDF is used in pregnancy without other antiviral drugs and outside the context of maternal HIV infection. In this study, 322 deliveries resulted in 323 live births (including two twin pairs and one stillbirth in the TDF arm). No difference was observed in birthweights between infants born to women who received TDF and those who received placebo: median birth weight was 3,028 g in the TDF arm and 3,061 g in the placebo arm.³²

Preterm Delivery

In the PROMISE trial, **there were no significant differences between** the TFV-based ART arm and the ZDV-based ART arms in the incidence of preterm delivery (delivery at <37 weeks; 18.5% vs. 19.7%, $P = 0.77$). However, TFV-based ART was associated with higher rates of very preterm delivery (delivery before 34 weeks; 6.0% vs. 2.6%, $P = 0.04$) and early infant death (4.4% vs. 0.6%, $P = 0.001$) than ZDV-based ART.²⁹ The greater number of early infant deaths was likely attributable to poor outcomes for very preterm infants in the settings where the trial

took place, but the higher rate of very preterm delivery in the TFV-based ART arm remains unexplained. Potential explanations include a lower than expected very preterm delivery rate in the ZDV-based ART arm or increased TFV exposure due to coadministration with LPV/r (LPV/r doses were increased in late pregnancy).

In contrast to the PROMISE trial results, the use of ZDV/3TC plus LPV/r was associated with a higher risk of preterm birth, very preterm birth, and neonatal death than TDF/FTC/EFV in the large observational study in Botswana.³³ **There was a higher risk of preterm delivery, however, for women who started treatment with TDF/FTC/EFV in the year prior to conception compared to women who started the same regimen late in the second trimester (adjusted risk ratio 1.33; 95% CI, 1.04–1.7).**²³

In a combined analysis of data from 4,646 births that occurred during the PHACS and P1025 studies, women who received TDF/3TC plus LPV/r and those who received ZDV/3TC plus LPV/r during pregnancy had no significant differences in the risks of preterm delivery overall (defined as a gestational age of <37 weeks) or very preterm delivery (<34 weeks).²⁶ **Among women with HIV who became pregnant and started ART while enrolled in serodiscordant couple PrEP studies, preterm birth (defined as live birth at <37 weeks gestation) occurred less frequently among women who received TDF (adjusted prevalence rate ratio [aPRR] 0.34, $P = 0.02$), and there was no difference in the rates of neonatal death (aPRR 0.68, $P = 0.6$).**³⁴

Additionally, in the trial of TDF 300 mg in Thai women with HBV (but not HIV), no difference was observed in the frequency of preterm delivery between the TDF and placebo arms: preterm delivery occurred for eight of 162 infants (5%) in the TDF arm (with none at <35 weeks), and 13 of 160 infants [8%] experienced preterm delivery in the placebo arm, including three infants (2%) who were delivered between 32 and 34 weeks gestation.³²

However, in an observational, multicenter, Canadian study of 2,787 mother-infant pairs in which the mothers received ART during pregnancy, the rate of preterm delivery (defined as delivery at <37 weeks) was significantly higher in mothers who received TDF-containing ART than in mothers who received ART that did not contain TDF (19.4% vs. 15.2%, $P = 0.024$). This higher rate of preterm delivery was not associated with whether the regimen also included a protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase strand transfer inhibitor.³⁵

In all, there remains some concern for a link between maternal TDF use and preterm birth or LBW, but the evidence is mixed; the role of concomitant medications and other cofactors and/or confounders requires further investigation.

Other Safety Data

Maternal Safety Outcomes

In a United Kingdom cohort of 71 pregnant women who were receiving TDF, retrospective analysis of serum creatinine and estimated glomerular filtration rate (eGFR) measured throughout pregnancy and 6 weeks after delivery revealed no decline in renal function during pregnancy and normal renal function (>90 mL/min) at 6 weeks postpartum (one woman's postpartum eGFR was 60 mL/min).³⁶

In the Thai trial in which pregnant women received TDF or placebo from a gestational age of 28 weeks to 2 months postpartum to prevent HBV transmission, there was no significant effect of maternal TDF use on maternal bone mineral density (BMD) 1 year after delivery.³⁷

Infant Safety Outcomes

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of TDF led to no increase in the likelihood of adverse infant metabolic, growth/development, cardiac, neurological, or neurodevelopmental outcomes.³⁸

In the DART trial described above, there were no differences in infant mortality between infants born to mothers who received TDF during pregnancy and those born to mothers who received other ARV drugs.²¹

Infant Growth Effects

In the U.S. PHACS study, there were no differences at birth in rates of LBW, SGA, or newborn LAZ and

HCAZ between infants who were exposed to combination drug regimens that contained versus didn't contain TDF; however, at age 1 year, infants exposed to combination regimens with TDF had a slight but significantly lower adjusted mean LAZ and HCAZ than those without TDF exposure (LAZ: -0.17 vs. -0.03, $P = 0.04$; HCAZ: 0.17 vs. 0.42, $P = 0.02$). There was no difference in weight-for-age z-score (WAZ). There were also no significant differences between infants with and without TDF exposure at age 1 year when defining low LAZ or HCAZ as ≤ 1.5 z-score. Thus, these slightly lower mean LAZ and HCAZ scores are of uncertain significance.²⁴ In the U.S. P1025 study, maternal TDF use was similarly not associated with differences in body size parameters at birth; however, among the 1,496 infants who were followed for 6 months, TDF exposure after the first trimester was associated with being underweight (WAZ <5%) at age 6 months (OR 2.06; 95% CI, 1.01–3.95, $P = 0.04$) when compared to no exposure.²⁵

A Kenyan cohort study also found an association between maternal TDF use (compared to ART without TDF) and lower infant 6-week WAZ despite no difference in infant weight at birth; however, TDF exposure was not associated with infant WAZ differences at age 9 months, and no associations were found with any other infant anthropometric measures at the 6-week or 9-month time points.³⁹ In the Dutch study of 74 HIV-exposed infants, maternal TDF use was linked to lower 6-month HAZ and WAZ after adjusting for differences in birthweight and prematurity.²⁸

On the other hand, results from a South African study demonstrated that the duration of *in utero* TFV exposure was not related to infant length at birth or to linear growth through the first 48 weeks of life.³¹ In the DART trial, there were also no differences in infant growth rates between infants born to mothers who received TDF during pregnancy and those born to mothers who received other ARV drugs.²¹

Finally, in the placebo-controlled trial that involved Thai women with HBV (but not HIV) who initiated TDF at 28 weeks gestation, there was no difference in growth outcomes at age 6 months between infants in the maternal TDF arm and infants in the placebo arm.³²

The evidence is inconsistent regarding the association between maternal TDF use during pregnancy and transient, small growth delays during the first year of life. These delays are of uncertain clinical significance.⁴⁰

Infant Bone Effects

In a cross-sectional study of 68 children aged 1 to 6 years who were exposed to HIV (but who were not infected) and who had *in utero* exposure to combination regimens that contained TDF ($n = 33$) or that did not contain TDF ($n = 35$), quantitative bone ultrasound measures and bone metabolism marker levels were similar for both groups.⁴¹ Another study evaluated whole body dual-energy X-ray absorptiometry scans performed within 4 weeks of birth among 74 infants who were exposed to >8 weeks of TDF *in utero* and 69 infants with no TDF exposure. The adjusted mean whole-body bone mineral content (BMC) was significantly lower in the TDF group (-6.5g, $P = 0.004$), as was the whole-body-less-head BMC (-2.6 g, $P = 0.056$).⁴² In a small, randomized trial that enrolled pregnant women in China with HBV/HIV coinfection, BMD and BMC at age 6 months were nonsignificantly lower in 14 TFV-exposed infants than in 13 infants who were not exposed to TDF.⁴³

On the other hand, in the randomized PROMISE trial, there was no difference in BMC between infants whose mothers received LPV/r-based ART with TDF and those whose mothers received LPV/r-based ART with ZDV.⁴⁴ In addition, in the Thai trial in which women with HBV (but not HIV) received TDF or placebo from a gestational age of 28 weeks to 2 months postpartum to prevent HBV transmission, there was no significant effect of maternal TDF use on infant BMD at age 1 year.³⁷

A study of 136 infants in Malawi whose mothers received TDF/FTC/EFV during pregnancy (with no control group for comparison) documented low-grade, transient abnormalities of serum phosphate and serum creatinine at ages 6 and 12 months.⁴⁵

The impact of maternal TDF use on infant bone mineral status remains uncertain and requires further longitudinal evaluation.

Excerpt from Table 8

Note: When using FDC tablets, refer to other sections in Appendix B and Table 8 for information about the dosing and safety of the individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations ^a	Use in Pregnancy
Tenofovir Disoproxil Fumarate (TDF) <i>Viread</i> (TDF/EFV/FTC) <i>Atripla</i> (TDF/3TC) <i>Cimduo</i> (TDF/FTC/RPV) <i>Complera</i> (TDF/DOR/3TC) <i>Delstrigo</i> (TDF/EVG/c/FTC) <i>Stribild</i> (TDF/EFV/3TC) <i>Symfi</i> (TDF/EFV/3TC) <i>Symfi Lo</i> (TDF/3TC) <i>Temixys</i> (TDF/FTC) <i>Truvada</i> Note: Generic products are available for some formulations.	TDF (Viread) <i>Tablet:</i> ^d • 300 mg <i>Powder:</i> • 40 mg/1 g oral powder TDF/EFV/FTC (Atripla): • TDF 300 mg/EFV 600 mg/FTC 200 mg tablet TDF/3TC (Cimduo): • TDF 300 mg/3TC 300 mg tablet TDF/FTC/RPV (Complera): • TDF 300 mg/FTC 200 mg/RPV 25 mg tablet TDF/DOR/3TC (Delstrigo): • TDF 300 mg/DOR 100 mg/3TC 300 mg tablet TDF/EVG/c/FTC (Stribild): • TDF 300 mg/EVG 150 mg/COBI 150 mg/FTC 200 mg tablet TDF/EFV/3TC (Symfi): • TDF 300 mg/EFV 600 mg/3TC 300 mg tablet TDF/EFV/3TC (Symfi Lo): • TDF 300 mg/EFV 400 mg/3TC 300 mg tablet TDF/3TC (Temixys): • TDF 300 mg/3TC 300 mg tablet TDF/FTC (Truvada): • TDF 300 mg/FTC 200 mg tablet	Standard Adult Doses <i>TDF (Viread)</i> Tablet: • TDF 300 mg once daily without regard to food Powder: • TDF 8 mg/kg daily (up to a maximum of TDF 300 mg). Take with food. <i>TDF/EFV/FTC (Atripla):</i> • One tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. <i>TDF/3TC (Cimduo):</i> • One tablet once daily without regard to food <i>TDF/FTC/RPV (Complera):</i> • One tablet once daily with food <i>TDF/DOR/3TC (Delstrigo):</i> • One tablet once daily without regard to food <i>TDF/EVG/c/FTC (Stribild):</i> • One tablet once daily with food <i>TDF/EFV/3TC (Symfi or Symfi Lo):</i> • One tablet once daily on an empty stomach and preferably at bedtime <i>TDF/3TC (Temixys):</i> • One tablet once daily without regard to food <i>TDF/FTC (Truvada):</i> • One tablet once daily without regard to food Pregnancy <i>PKs in Pregnancy:</i> • AUC is lower in third trimester than postpartum, but trough levels are adequate. <i>Dosing in Pregnancy:</i> • No change in dose is indicated. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, COBI, DOR, EFV, EVG, FTC, RPV)	High placental transfer to fetus. ^b No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Studies in monkeys (at doses approximately 2-fold higher than those for human therapeutic use) show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy. Human studies demonstrate no consistent link to low birth weight, but data are conflicting about potential effects on growth outcomes later in infancy. If patient has HBV/HIV coinfection, it is possible that an HBV flare may occur if TDF is stopped; see Hepatitis B Virus/HIV Coinfection . Renal function should be monitored because of potential for renal toxicity.

^a Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10](#)).

^b Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

^d Generic product is available.

Key: 3TC = lamivudine; ARV = antiretroviral; AUC = area under the curve; COBI = cobicistat; DOR = doravirine; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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